U.S. EPA EXPERT ELICITATION STUDY ON THE CONCENTRATION-RESPONSE RELATIONSHIP BETWEEN ANNUAL AVERAGE AMBIENT $PM_{2.5}$ EXPOSURES AND ANNUAL MORTALITY

Pre-Elicitation Workshop Summary

January 20, 2006

INTRODUCTION

The purpose of this workshop was to assemble the panel of experts participating in EPA's expert elicitation study on the concentration-response (C-R) relationship between annual average ambient fine particle ($PM_{2.5}$) exposures and annual mortality. The workshop was intended to educate the experts about expert judgment and about the elicitation process, as well as foster exchange among the participants about the key evidence available to answer questions in the elicitation interview protocol.

The purpose of this summary is to provide an overview of the discussions at the workshop for participants and for those who could not attend the workshop. The views expressed at the workshop are the opinions of the speaker only. Each expert participating in this study may choose to consider these views if he wishes along with his own views concerning data and issues critical to developing his individual distribution. The workshop was not intended to promote consensus with in the group, but rather to share ideas among experts and discuss evidence for or against such ideas.

SUMMARY

Introductory Remarks

- John Bachmann and Lydia Wegman of EPA's Office of Air Quality Planning and Standards (OAQPS) spoke to the group about the importance of the project and some ways in which the results might be used, such as in assessing benefits of future air quality standards.

- Lisa Conner, the EPA project team lead, reviewed the objectives for the day and the workshop agenda. She also introduced the project team to the group. (Note that team members are indicated with an asterisk next to their name in the list of participants at the end of this document).

- Ms. Conner then explained the regulatory setting and motivation for the study. She said that the 2002 National Academy of Science (NAS) report, *Estimating the Public Health Benefits of Proposed Air Pollution Regulations* (NRC, 2002) recommended the use of expert elicitation in uncertainty characterizations and was one of the motivating factors for this study. She described a pilot study that was done in 2003 and 2004 as a pre-cursor to this expanded study. She explained some of the peer review comments received on the pilot study and how this elicitation study is addressing those concerns, such as increasing the sample size and including more interaction between experts. In addition, she reviewed how the results of the elicitations might be used in future benefits analyses (see Chapter 4 of U.S. EPA, 2005 for further details).

- Some experts wondered about the purpose of the post-elicitation workshop. Dr. Katy Walker, an elicitation specialist with Industrial Economics (IEc), told the group that the purpose was not to promote consensus among the panel, but to allow experts to discuss points of agreement and disagreement; to consider evidence that they may not have relied on in making their judgments; and to adjust their responses following the workshop if they felt it was appropriate.

<u>Primer on Expert Judgment</u>

- This portion of the workshop began with the experts completing an exercise consisting of six questions on a variety of subjects to illustrate the process of expert judgment. The exercise asked the experts for their 5th, 50th, and 95th percentiles for each quantity.

- Dr. Walker reviewed applications of expert judgment from different scientific disciplines. She then explained the types of evidence that can be used to form expert judgments and reviewed methods used to judge the quality of this evidence. She then described the concept of calibration and measuring the quality of expert judgments. Finally, she explained the heuristics and biases that often affect experts' subjective judgments and reviewed ways to avoid these pitfalls.

- Dr. Walker then reviewed the answers to the exercise, displaying the experts' responses to see how they compared to the actual answers. She indicated that the purpose of the exercise was to demonstrate the kind of probabilistic judgments that experts would be expected to make during the elicitation interview and to see whether the responses revealed any use of the heuristics discussed. The results of the exercise showed that the experts were generally consistent in their ability to capture the correct answer within their uncertainty bounds, particularly on questions related to air pollution.

<u>Explanation of the Interview Process</u>

- Dr. Pat Kinney, who is servings as the domain (i.e. subject matter) expert on the elicitation team, provided an overview of the elicitation process. He described the goals of the interview, the role of the elicitation team during the interviews, and the purpose for the post-elicitation workshop.

- Dr. Kinney then reviewed the purpose for the protocol, the protocol structure, and the main quantitative question. He indicated that experts would be asked to characterize their estimate of the percent change in annual mortality due to a 1 $\mu g/m^3$ reduction in ambient annual average $PM_{2.5}$ as a probability distribution, rather than a point estimate.

- An expert asked how to incorporate the time course of the change in mortality into the quantitative estimates. Dr. Kinney clarified that the protocol is asking about a new steady-state mortality rate, and therefore experts did not need to take the time course into consideration. He also indicated that this topic is handled separately in EPA's benefits calculation (see EPA, 2005).

- Henry Roman, the IEc project manager, provided an overview of the resources available to experts before and during the elicitation interviews. He indicated that experts were provided with a CD containing papers relevant to the quantitative question in the protocol. He also said experts were given a list of recently published papers compiled by EPA's National Center for Environmental Assessment (NCEA) that were not included in the *Air Quality Criteria for Particulate Matter* (EPA, 2004).

- An expert asked if the he could provide studies to the elicitation team that he felt were important for making their quantitative judgments that could then be distributed to the rest of the panel. Mr. Roman encouraged the experts to share any evidence that they felt was relevant with the group.

- Mr. Roman then told the group that a set of background technical information pages containing relevant maps, data, and regulatory information would be available to assist the experts. Finally, he reviewed two spreadsheets that could be used during the interviews to provide real-time feedback to the experts on their quantitative estimates. He described several ways that experts could express their quantitative judgments such as by providing a single distribution characterizing the percent change in mortality per unit change in $PM_{2.5}$ for the range suggested by the study (4-30$\mu g/m^3$), or providing separate distributions for specific intervals within the range (e.g., a piece-wise linear function). In addition, he demonstrated options for incorporating assumptions about causality and threshold into the C-R function. He demonstrated how experts could incorporate causality and threshold directly into the distribution, or how they could provide a distribution conditional on assumptions about causality and threshold. The elicitation team could then combine these elements using a Monte Carlo simulation. Finally, he said that the spreadsheets could also perform "back of the envelope" calculations of the expected annual mortality in the U.S. based on the experts' C-R function to serve as a reality check.

- An expert said he might want to rely on the estimates from the American Cancer Society (ACS) study (Pope et al., 2002) when providing his C-R function. However, he felt that they were biased low because the cohort had higher than average educational attainment. He felt that if the ACS study results could be adjusted by a factor to account for the difference in education between the cohort and the U.S. population, the results would be more accurate. He wondered if the elicitation team could provide this type of adjustment during the interview.[1]

- Another expert thought it would be possible to create interaction terms for socioeconomic status and particulate matter (PM) to generate an adjusted coefficient for the effect in the national population. He also thought that exposure misclassification was an important issue to probe during the interviews. He mentioned two published reanalyses of the ACS cohort data. The first restricted the cohort to those living in the same county as the air pollution monitor (Jerrett et al., 2003) and the second used geocoding to more closely approximate exposure (Jerrett et al., 2005). He pointed out that both of these studies yielded higher results than the original ACS study.

Protocol Feedback

- The group discussed the elicitation protocol, beginning with reviewing the assumptions underlying the quantitative question in Part 2. One expert expressed concern about the assumptions pertaining to co-pollutant concentrations. He felt that all of the mortality changes due to PM are not all due to PM alone and therefore, co-pollutant concentrations may affect the magnitude expressed in the C-R function.

- Dr. Bryan Hubbell clarified that EPA was interested in eliciting a C-R function for $PM_{2.5}$–related mortality only. He indicated that other efforts within the agency were underway to determine the health effects of other pollutants. However, he encouraged experts to describe any factors that have a significant effect on their quantitative estimates, including co-pollutants.

- An expert was concerned that the assumptions outlined in Section 2 of the protocol do not specify the nature of the regulation and pointed out that reducing emissions from power plants for example, would reduce certain $PM_{2.5}$ components, while reducing motor vehicle emissions would reduce others. Dr. Hubbell indicated that the experts should assume, for the purpose of this exercise, that the regulatory action would achieve proportional reduction in all $PM_{2.5}$ components. Mr. Roman indicated that a change to the protocol assumptions would be made to clarify this issue.

- Dr. Kinney indicated that experts could incorporate their uncertainties about components by widening the bounds of their concentration-response (C-R) function distribution. John Bachmann also added that EPA is interested in examining the compositional effects of $PM_{2.5}$ in the future but that this issue is not the focus of this study.

[1] Note that experts are welcome to use available data to develop such estimates in advance of the interviews or during the interview process.

- An expert was concerned that the experts who were not present at the workshop would not have the benefit of the clarifications of the assumptions in the protocol. Dr. Walker said that the elicitation team would email all of the experts the presentation slides, as well as a written summary of the workshop. She also indicated that for those experts not able to attend the workshop, she would take additional time in the beginning of the interview to ensure that all of the assumptions in the protocol were clear.

Topic Discussions

This portion of the workshop consisted of structured discussion sessions on three topics related to the PM/mortality issue. For each topic, one expert presented evidence related to the issue being discussed, and two other experts served as discussants.

The purpose of these sessions was to foster exchange among the participants about the key evidence that should be considered in giving a judgment about each issue. The goal was to share evidence among the group so that expert could better understand its strengths and limitations, rather than to encourage a consensus within the group.

Topic 1 - Evidence For/Against a Causal Relationship

- The main presenter for Topic 1 felt that there were two issues to consider when determining if a relationship is causal: 1) the possibility that the observed effect is due to confounding, and 2) existence of biologic mechanisms. He pointed out that the fact that associations persist across study designs (e.g., cohort, time-series, intervention) decreased the possibility that the effects were due to confounding, since different designs are associated with different vulnerabilities. He also thought that since studies with better exposure assessment relative to the ACS study showed higher effect estimates (e.g., Dockery et al., 1993, Jerrett et al., 2005, Hoek et al., 2002), it was likely that the relationship is causal. Finally, he pointed to epidemiologic and animal studies that support a link between air pollution and risk factors for cardiovascular disease, such as atherosclerosis and plaque stability.

- The first discussant on this topic felt that animal studies were supportive of a causal relationship between PM and mortality. He described a set of subchronic studies where normal and compromised mice were exposed to concentrated ambient particles (CAPs) or filtered air. He indicated that the CAP exposure caused changes in heart rate and heart rate variability. It also accelerated plaque development and affected plaque characteristics. He pointed out that animal studies had the ability of isolating the PM effects by administering concentrated particles from the ambient air in a controlled environment.

- The second discussant on this topic felt that there was sufficient evidence to infer that there is a causal mechanism. However, he thought the unresolved issue with respect to causality was whether available estimates explain the true relationship between PM and mortality, since evidence exists indicating that other pollutants may cause a portion of the effects associated with PM. He cited evidence showing that non-PM components can cause lung inflammation, as well as animal studies comparing health endpoints resulting from exposure to unfiltered and filtered "fresh" emissions. In some cases, similar effects were seen before and after filtration (i.e., removal of PM had no effect on the outcome). In other cases, effects were seen for both filtered and unfiltered emissions (i.e., PM appears responsible for some, but not all of the effects of fresh emissions). Additionally, he discussed some studies that only found effects from the unfiltered emissions (i.e., PM appears responsible for all of the effect). Therefore, he felt that there was remaining uncertainty as to whether some of the mortality effects currently attributed to $PM_{2.5}$ may be due to other pollutants.

- One expert wondered how much transformation occurs in the fresh emissions by the time an individual is exposed to them. Discussant #2 indicated that substantial transformation was likely to occur between the emission source and the receptor. The expert then expressed the opinion that studies examining effects of fresh emission might be most relevant when examining mortality outcomes related to traffic sources, but not as relevant when examining mortality outcomes related to long-term ambient PM exposures.

- Another expert pointed out the possibility that particles may serve as a vehicle for the penetration of co-pollutants into the lungs (i.e., there would be less of an effect seen from co-pollutants if particles were not present). Discussant #2 agreed but was not convinced that particles were responsible for all of the observed effects; he thought decreasing particles might proportionally decrease the effects of co-pollutants. He also thought that these co-pollutants increased the uncertainty in the C-R function.

- Another expert thought it would be interesting to hear a skeptic's point of view on causality. He suggested that the group discuss the main arguments that they had heard against a causal relationship. Discussant #2 felt that most arguments against causality were related to measurement error. Another expert said that lack of control for confounding was often an issue cited by critics. A third expert added that he had heard the argument that the relative risks (RRs) were not large enough to indicate a real effect since the errors are often larger than the effects themselves.

Topic 2 – Shape of the C-R Function

- The main presenter for Topic 2 first pointed out that benefits analysis can potentially analyze PM levels down to background level (3-5 $\mu g/m^3$), but the lowest values seen in epidemiologic studies are around 12 $\mu g/m^3$. He presented estimates from epidemiologic studies examining the C-R function between PM and mortality. Generally, he felt that the evidence supported a linear, non-threshold model. He pointed out that no evidence for a threshold has been found at the lowest observed levels in epidemiologic studies, although the uncertainty in the C-R function increased at these levels.

- Discussant #1 for this topic discussed the results of an extended follow-up of the Six Cities study aimed at describing the C-R function. Utilizing an approach similar to that used by Dr. Louise Ryan to evaluate a dose-response relationship for arsenic, he noted that the Six Cities researchers fit 32 possible models to the data and then calculated a weighted Bayesian model average. The results of this averaging process indicated a linear C-R function. In addition, when the errors were combined across all of the models using the Jackknife technique, the data supported a linear relationship that extended to PM levels as low as 10 $\mu g/m^3$.

- Discussant #2 on this topic felt that the observed overall C-R curve is a composite of several curves for subpopulations of varying susceptibility. He presented evidence from several cohort studies showing a linear, non-threshold model. In addition, he felt that toxicological studies suggest that PM promotes oxidative lung damage, aortic plaque development, and vascular inflammation. He also presented evidence from studies on smoking and atherosclerosis that show a linear dose-response relationship. He thought issues that added to the uncertainty in the C-R function shape included exposure characterization error, lack of data in the low and high ends of the range of PM exposures, differing C-R functions by components, and differences in acute and long-term effects.

- An expert indicated that studies on children's lung function and population-based ecological studies show no evidence of a threshold. He then presented a figure containing the C-R functions from four studies on the same scale, each of which included a different number of cities and varying ranges of PM exposures. He pointed out that all of the slopes look similar and none of them provide evidence of a threshold.

Topic 3 - Quantitative Estimates of the $PM_{2.5}$-Mortality Effect for the US Population

- The main presenter for Topic 3 presented a chart showing estimates and confidence bounds for several epidemiologic studies to show their relative magnitude. He also thought that there is no evidence for the existence of a threshold in the C-R function, stating that an analysis on the ACS cohort study data looking only at exposures below 15 $\mu g/m^3$, showed statistically significant results. He indicated that the magnitude of the C-R function might be affected by education, since results from the ACS cohort stratified by education level showed higher estimates for those with less than a high school education. In addition, he thought that exposure misclassification affected the magnitude of the C-R function, pointing out that populations with less accurate exposure estimates show lower risk estimates. He also thought that the past five years were the most influential for causing mortality effects. He concluded by saying that he felt that the effect estimate that he would put the most weight on would be the ACS extended analysis, stratified by education level.

- Discussant #1 on this topic began by comparing effect estimates from three studies estimating mortality over different exposure periods: a time-series study with one day of exposure (Samet et al., 2000a & 2000b), a cohort study with one year of exposure (Pope et al., 2002), and a cohort study with 10 years of exposure (Dockery et al., 1993). He felt that this comparison suggested a trend of increasing effect estimates with longer exposure periods. He then said he thought the differences between the Six Cities cohort and ACS cohort effect estimates were due to differences in the quality of exposure estimates. He pointed out that the ACS study assigned exposures to subjects by metropolitan area, whereas the Six Cities study assigned exposures to subjects by county. A recent reanalysis of ACS cohort members living in southern California with exposures assigned by zip code showed higher effect estimates (Jerrett et al., 2005). Finally, a study in the Netherlands, with exposures measured by residential address, found effect estimates that were slightly higher than the Six Cities data. Further evidence he thought was important to consider when quantifying the C-R function included intervention studies examining mortality rates during periods of a sharp decline in air pollution. In addition, he felt that similarity found between the city-specific slopes in the original Six Cities cohort study and the extended follow-up of the Six Cities cohort gives weight to the effect estimates from that cohort.

- Discussant #2 on this topic stated that the Six Cities and ACS studies should not necessarily be considered competing studies. He thought that there could be several factors to explain why the ACS effect estimate is lower than the Six Cities estimate, including differences in educational attainment between the ACS cohort and the general population, less precise exposure estimates, and differential migration. He told the group that the primary ACS effect estimates increase by one third when adjusted to account for differences in educational attainment between the ACS cohort and the Six Cities cohort.

<u>Wrap Up</u>

Two main topics were discussed in the wrap-up session.

- First, an expert expressed lingering concern that the effect of this workshop and the post-elicitation workshop would be to bring the experts in attendance closer to a consensus view, even if that was not its stated purpose. The elicitation team indicated that it would review the results for the experts who attended the workshop to see if they were similar to each other, and if they differed from the experts who did not attend the workshop.

- Ms. Conner then asked IEc to describe the expert selection process. Mr. Roman explained that that the process had two parts, both of which relied on peer nominations. In the first part, IEc sought nominations from experts identified from a publication count. These experts were separated into four groups, and each group was asked to focus on different criteria (generally most knowledgeable about the effects and their uncertainty, significant contributions to the study of mechanisms, experience on panels and conducting risk assessment of PM in a policy context, and performing cutting-edge research on PM-related mortality). IEc intended to take the two most highly nominated experts from each category, plus one highly nominated individual from the group at large. While there was a fairly good acceptance rate, Mr. Roman noted that the process yielded a group with less diversity in expertise than was intended, as most of those who were selected and agreed to participate were epidemiologists. In an effort to increase representation of other disciplines, EPA sought additional nominations of experts in the biological, medical, and toxicological fields from members of the Health Effects Institute (HEI) Research and Review committees. IEc invited three experts from this list following a random ordering process, for a total of 12 experts. Mr. Roman noted that the acceptance rate for this second step was not as high; in both cases, the most frequently cited reason for declining was scheduling concerns given the level of commitment asked of the experts.

Sources

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+ Dr. Utell participated via teleconference for a portion of the workshop.